Review paper

Left atrial compliance: an overlooked predictor of clinical outcome in patients with mitral stenosis or atrial fibrillation undergoing invasive management

Joanna B. Hrabia[1], Elahn P.L. Pogue[1], Alexander G. Zayachkowski[1], Dorota Długosz[1], Olga Kruszelnicka[2], Andrzej Surdacki[3], Bernadeta Chyrchel[3]

[1]Students' Scientific Group at the Second Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland
[2]Department of Coronary Artery Disease and Heart Failure, The John Paul II Memorial Specialist Hospital, Krakow, Poland
[3]Second Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland

Adv Interv Cardiol 2018; 14, 2 (52): 120–127
DOI: https://doi.org/10.5114/aic.2018.76402

Abstract

In the assessment of cardiovascular disease, the clinical significance of left atrial (LA) pressure-volume relations has largely been overlooked in contrast to left ventricular (LV) compliance. However, LA compliance has recently gained more attention. Net atrioventricular compliance (*Cn*), a joint measure of LA and LV compliance, can be calculated non-invasively by a previously validated method using parameters from standard echocardiography. Compliance measurement may be of relevance in selected clinical settings. First, subjects with low *Cn* are more likely to have their mitral valve area overestimated by the traditional mitral pressure half-time method. Consequently, low *Cn* in mitral stenosis, usually resulting from reduced LA compliance, can be mistaken for mild mitral stenosis. Second, low *Cn* independently predicted pulmonary hypertension and disease progression in medically treated mitral stenosis, and late cardiovascular complications after successful percutaneous mitral valvuloplasty. Decreased LA compliance also accounts for stiff LA syndrome, a rare complication of radiofrequency catheter ablation for atrial fibrillation, manifesting as otherwise unexplained heart failure with elevated LA pressure and pulmonary hypertension. Finally, depressed pre-ablation LA stiffness index, i.e. the ratio of the change in LA pressure to the corresponding change in LA volume during passive LA filling, was an independent predictor of arrhythmia recurrence. Thus, LA stiffening translates into adverse clinical outcomes in patients with mitral stenosis or atrial fibrillation undergoing interventional procedures. Whether reduced LA compliance after LA appendage occlusion can result in the LA stiff syndrome, has not been reported so far.

Key words: mitral stenosis, radiofrequency catheter ablation, percutaneous mitral valvuloplasty, percutaneous left atrial appendage closure, left atrial compliance.

The concept of net atrioventricular compliance, a joint measure of left atrial and left ventricular compliance

As early as 30 years ago, Thomas *et al.* [1] demonstrated that in the setting of acute mitral valvotomy, mitral pressure half-time ($T_{1/2}$) (the time required for the transmitral pressure gradient to fall to half of its maximal early diastolic value), traditionally perceived as an inverse measure of mitral valve area (MVA) [2], lost its predictive accuracy after percutaneous balloon mitral valvuloplasty (PBMV). In fact, the data showed essentially no correlation between $T_{1/2}$ and MVA immediately after valvotomy. These findings strongly suggested that acute changes in other hemodynamic variables are likely to play a role in the breakdown of the traditional method for determining MVA from $T_{1/2}$ directly after dilation of a stenotic mitral valve [1]. Therefore, they proposed estimation of the net atrioventricular compliance (*Cn*) in order to overcome this limitation. In brief, this concept was based on the following considerations with regard to early LV filling.

Both LV compliance (*Cv*) and LA compliance (*Ca*) are described by the classical equations:

$$Cv = dV_v/dp_v \text{ and } Ca = dV_a/dp_a,$$

where V and p represent volume and pressure, respectively, in the LV (V_v and p_v) and the LA (V_a and p_a).

Unfortunately, direct measurements of LA and LV pressures are extremely rare in clinical practice. However,

Corresponding author:
Bernadeta Chyrchel MD, PhD, Second Department of Cardiology, Jagiellonian University Medical College, 17 Kopernika St, 31-501 Krakow, Poland, phone: +48 509 257 665, e-mail: bernadeta.chyrchel@onet.pl
Received: 13.04.2018, **accepted:** 29.04.2018.

we can easily measure transmitral blood flow by Doppler echocardiography, thereby also estimating transmitral pressure gradient by the Bernoulli formula. Additionally, absolute values of changes in LA and LV volume during early LV filling can be assumed equal, if we neglect blood flow from pulmonary veins into the LA during early LV filling ($dV_v = -dV_a$).

According to Thomas *et al.* [1], net atrioventricular *Cn* is defined as the ratio of the rates of change in ventricular volume (V_v) and transmitral pressure difference ($\Delta p = p_a - p_v$) during early LV filling:

$$Cn = -dV_v/d\Delta p,$$

with the negative sign arising because an increase in LV volume is associated with a decrease in transmitral pressure gradient [3].

Notably, *Cn* is related to *Cv* and *Ca* as: $1/Cn = 1/Cv + 1/Ca$, in analogy to two capacitors connected in series, and *Cn* is lower than *Ca* and *Cv*.

On the basis of in vitro modeling of transmitral flow, Newton's second law of motion and the continuity equation with some simplifying assumptions and the integration of several equations, Thomas *et al.* [1] derived a modified approximate formula linking effective MVA to mitral $T_{1/2}$:

$T_{1/2}$ [ms] = 11.6 × *Cn* [ml/mm Hg] × $(\Delta p_0)^{1/2}/MVA$ [cm^2],

where *Cn* represents net atrioventricular compliance and Δp_0 [mm Hg] is the maximal transmitral pressure gradient during early LA filling.

The simplifications, shown as allowable in the *in vitro* model, encompassed inclusion of the LA and pulmonary veins in a common chamber, ignoring LV active relaxation, neglecting viscous mitral resistance with consequent use of the simplified Bernoulli equation for the transmitral pressure gradient-flow velocity relationship, and constant *Cn* during early LV filling owing to opposite changes in LA and LV compliance [1].

The authors [1] also confirmed the superiority of this novel formula over the traditional equation ($T_{1/2} = 220/MVA$) [2], validating it in patients after mitral valvotomy, thereby emphasizing the importance of simultaneous changes in LA and LV compliance chamber compliance after valvotomy for the accuracy of MVA calculations from $T_{1/2}$. Keeping in mind the simplified relationship between transmitral pressure gradient (Δp) and flow velocity (v), the formula can be transformed into another form, as demonstrated by Flachskampf *et al.* [3]:

$$Cn \text{ [ml/mm Hg]} = -1270 \times MVA \text{ [cm}^2\text{]}/dv/dt.$$

Consequently, because dv/dt may be approximated by the deceleration rate of the early transmitral flow velocity profile (E-wave), the formula can finally be re-expressed [4] as:

$$Cn \text{ [ml/mm Hg]} = 1270 \times MVA \text{ [cm}^2\text{]}/\text{E-wave downslope [cm/s}^2\text{]}.$$

Importantly, effective MVA can be estimated either by the continuity equation [3] or planimetry [5], both of which may be used based on standard echocardiography in real-world patients.

As mentioned before, *Cn* is influenced by both *Ca* and *Cv*. This can result from either LV or LA stiffening (or both), i.e. with the LV or LA operating on their respective steeper pressure-volume curves. Accordingly, LV stiffening would lead to a more rapid increase in LV pressure during early LV filling, while LA stiffening would accelerate a simultaneous fall in LA pressure. Both these effects would translate into a decreasing transmitral pressure gradient, a driving force of LV filling, thereby reducing peak transmitral velocity during the early LV filling phase. These effects would predominate if changes in *Ca* or *Cv* did not trigger activation of compensatory mechanisms aimed at the preservation of LV filling volume and stroke volume. However, Thomas *et al.* [6] showed, by means of their complex mathematical model of LV filling, that if we allow LA pressure to change in order to keep the LV filling volume constant, lower LA or LV compliance results in increased, not decreased, E-wave peaks, and an elevated E-wave deceleration rate. This is equivalent to a more restrictive profile of early LV filling, commonly observed in patients with impaired LV compliance and explained by higher LA pressure to maintain LV stroke volume. Additionally, an increased E-wave deceleration rate corresponds to lower *Cn*, calculated as MVA divided by the E-wave slope. Therefore, the mathematical models of early LV filling [1, 6], despite their inherent assumptions, simplifications and limitations, provide a good description of phenomena observed in clinical practice.

Low net atrioventricular compliance – a predictor of pulmonary hypertension, exercise intolerance and disease progression in mitral stenosis on medical therapy

As a practical clinical application of the above-presented method of *Cn* assessment, Schwammenthal *et al.* [4] demonstrated that low *Cn*, but not MVA, predicted not only resting systolic pulmonary artery pressure (PAP), but especially the magnitude of its exercise-induced rises in patients with moderate or severe mitral stenosis. In addition, subjects with low *Cn* (≤ 4 ml/mm Hg, lower tertile) were more symptomatic and, importantly, much more likely to have their MVA overestimated by the $T_{1/2}$ method compared to MVA computed from the continuity equation or planimetry. Consequently, low *Cn*, usually resulting from low LA compliance, the main determinant of *Cn* in clinically relevant mitral stenosis, can be mistaken for mild mitral stenosis and these patients may be deprived of potential benefits of mitral valvotomy owing to a false diagnosis of non-severe mitral stenosis [4].

Pulmonary hypertension is recognized as a classical tool to assess the severity of disease in patients with mitral stenosis. Curiously, systolic PAP at rest varies

among patients presenting with similar levels of mitral obstruction, which highlights the importance of non-valvular factors for hemodynamic consequences of mitral stenosis. Interestingly, Li *et al*. [7] found that low *Cn* was a major independent predictor of LA pressure and systolic PAP measured by cardiac catheterization in patients with severe pure mitral stenosis.

More recently, Nunes *et al.* [8] studied 140 patients with rheumatic mild-to-severe mitral stenosis (mean *MVA*: 1.2 ±0.4 cm^2), excluding all subjects with factors that could have potentially otherwise influenced pulmonary pressure. Low *Cn*, high mean transvalvular gradient, and small MVA were the only factors influencing systolic PAP in multivariate regression irrespective of their mutual relations. Additionally, polling all the study subjects together, only 18% of the patients with a *Cn* level above a cut-off > 4 ml/mm Hg were referred for an interventional therapy (percutaneous or operative), while in those with a *Cn* below or equal to this cut-off value, the respective proportion was as high as 82% over a median follow-up of 22 months. However, from the clinical point of view, perhaps an even more relevant feature of *Cn* could be an ability to predict clinical outcome in a subset of the mitral stenosis patients who presented asymptomatically [8]. In 52 initially asymptomatic patients with moderate or severe mitral stenosis, mitral stenosis-related interventions were performed in 30% and 69% of the former (i.e. *Cn* > 4 ml/mm Hg) and the latter (i.e. *Cn* ≤ 4 ml/mm Hg) subgroup, respectively, based on a complex clinical assessment encompassing functional status, mitral orifice obstruction severity and PAP, in agreement with practice guidelines. Notably, this association between low *Cn* and a clinical need for interventional therapy retained its additional and incremental predictive effect in addition to classical indices of mitral stenosis, including valve area, transmitral pressure gradient and PAP [8].

Jung *et al.* [9] demonstrated that also *Cn* changes in response to exercise may be clinically relevant. Patients with asymptomatic moderate rheumatic mitral stenosis (*MVA*: 1.0–1.5 cm^2) who developed clinically relevant dyspnea during symptom-limited exercise echocardiography exhibited significantly greater early-exercise induced decreases in *Cn* at a workload of 50 W than those who did not present exertional dyspnea, averaging 70% vs. 50% for relative *Cn* reductions, respectively. Moreover, although *Cn* and systolic PAP were inversely related both at rest and during peak exercise, the relative *Cn* decrease at 50 W, but not MVA, was the only independent determinant of exercise intolerance after adjustment for systolic PAP at peak exercise and its relative increases at 50 W [9]. Thus, these findings may aid physicians in furthering their understanding of the pathophysiology behind mitral stenosis, with a focus beyond obvious valve-related factors. As decreased LA compliance corresponds to a more pronounced rise in LA pressure for a given increment in LA volume, this is likely to be a mechanistic basis of the contribution of the properties of the LA wall to the development of complications surrounding mitral stenosis. Additionally, *Cn* can provide prognostic value for patients with mitral stenosis and may additionally help in monitoring and assessing the risk in asymptomatic patients with early-stage disease.

Low net atrioventricular compliance – a predictor of late cardiovascular complications in mitral stenosis after successful percutaneous balloon valvuloplasty

In 150 patients with symptomatic moderate or severe mitral stenosis, Mahfouz *et al.* [10] demonstrated that low baseline *Cn* (≤ 3.75 ml/mm Hg) was associated with higher transmitral pressure gradient, mean LA pressure and systolic PAP assessed after, but not before, successful PBMV. Additionally, upon conducting a follow-up over a median of 32 months, they found that patients with baseline (i.e. pre-procedural) *Cn* ≤ 3.75 ml/mm Hg had a higher incidence of a composite adverse outcome, including cardiovascular death, hospitalization for decompensated heart failure, mitral valve reintervention, systolic PAP re-elevation, newly developed atrial fibrillation and worsening of right ventricular function. These findings can be attributed to the fact that, inasmuch as LA compliance contributes to *Cn*, low *Cn* appears to reflect fibrosis and stiffening of the LA wall, probably owing to a chronic rheumatic process affecting the LA myocardium [10]. So, patients with a lower *Cn* are likely to have persistently worsened LA function, in turn increasing the risk of late adverse outcomes despite successful PBMV.

Additionally, Nunes *et al.* [11] showed that low *Cn* was an independent predictor of both cardiovascular death and all-cause mortality combined with mitral valve reinterventions in 427 patients following PBMV for severe mitral stenosis followed for a median of 31 months. They also demonstrated that pre-PBMV *Cn* ≤ 4 ml/mm Hg, when incorporated into a 5-year mortality risk prediction model, significantly improved its ability to identify patients at risk of late cardiovascular death. This may be related not only to persistent dysfunction of the LA by itself, when the LA operates on a steeper portion of its pressure-volume curve with consequent backward transmission of elevated LA pressure, as suggested previously [10]. Low *Cn* can also coexist with long-lasting changes of the pulmonary vasculature, which often does not reverse despite a successful valvuloplasty, resulting in the continued elevation of pulmonary vascular resistance in the years following the procedure [11]. These irreversible changes may include not only pulmonary arteries, but also veins exposed to chronically elevated pressure. In fact, the concept of *Cn* was based on a model of early LV filling, where LA and pulmonary veins are assumed to

be a common elastic chamber receiving all the cardiac stroke volume during systole and discharging it passively through the mitral valve into the LV in diastole [1]. Thus, this assumption implies that elastic properties of pulmonary veins also affect *Cn*.

Accordingly, *Cn* measurement, in addition to conventional clinical and echocardiographic characteristics, can provide a better insight into potential benefits of PBMV on an individual basis in patients referred for this procedure. Hence, physicians can more accurately identify those who are at higher risk of developing late adverse cardiovascular outcomes despite successful PBMV.

Stiff left atrial syndrome – a rare complication of radiofrequency catheter ablation for atrial fibrillation

Atrial fibrillation has been linked to atrial enlargement, having a close correlation with electrical and structural remodeling of both atria. Interestingly, reductions in both LA and right atrial volume were observed in patients 6–12 months after radiofrequency catheter ablation (RFCA) [12, 13]. Moreover, this effect was independent of whether AF recurred during the follow-up [12, 13]. Notably, Choi *et al.* [14], comparing patients who had maintained sinus rhythm 3 months after either RFCA or electrical cardioversion, reported more significant decreases in LA volume in the former than in the latter subgroup. Furthermore, Witt *el al.* [15] estimated that about 8% of patients undergoing RFCA exhibited rises in right ventricular systolic pressure exceeding 10 mm Hg 3 months after ablation compared to pre-ablation values, and ascribed it to reduced LA compliance with consequent otherwise unexplained pulmonary hypertension, a basis of LA stiff syndrome. In their experience [15], the RFCA-induced increase in right ventricular systolic pressure was associated with a more restrictive profile of post-ablation, but not pre-ablation, LV filling, a likely consequence of elevated LA pressure, thereby mimicking more pronounced LV diastolic dysfunction. In a study aimed at explaining these changes, Hof *et al.* [16] performed a magnetic resonance imaging (MRI) study of 206 patients who received pulmonary vein isolation during RFCA. The report showed post-ablation LA fibrosis in as many as 77% of a subgroup of 52 subjects who underwent late enhancement MRI, despite absent fibrosis in the regions of interest prior to RFCA. In addition, maximal LA volume decreased irrespective of fibrillation recurrence, which suggests a close relationship between LA fibrosis and reduced LA volume after RFCA [16].

The concept of the stiff LA syndrome was first proposed by Pilote *et al.* [17], who described a 67-year-old woman presenting 7 years after mitral valve replacement with pulmonary edema and severe right ventricular heart failure despite no prosthetic valve dysfunction, coupled with pulmonary hypertension and large V-waves on pulmonary capillary wedge pressure tracing, and calcification lesions in the LA wall on autopsy. In a large prospective study of 1380 consecutive patients referred for RFCA, Gibson *et al.* [18] described the stiff LA syndrome in 19 (1.4%) subjects, and identified severe pre-operative LA scarring (defined as an absence of voltage on bipolar LA electrograms and validated by electroanatomic mapping), diabetes and obstructive sleep apnea as its independent predictors. That lower pre-procedural LA size and higher mean LA pressure were also independently related to future occurrence of the syndrome might have indirectly suggested decreased compliance of the LA operating on a steeper pressure-volume curve [18].

Accordingly, the stiff LA syndrome, a rare complication of RFCA or cardiac surgery, is now recognized as new-onset dyspnea in the absence of significant LV dysfunction, constrictive pericarditis, worse than mild mitral valve disease or pulmonary vein stenosis – accompanied by pulmonary hypertension, elevated mean LA pressure and large V-waves ≥ 10 mm Hg above the mean LA pressure (or > 7 mm Hg above the mean pulmonary wedge pressure) on invasive pressure tracings [18–20]. The above presented clinical constellation is ascribed to reduced LA compliance, which accounts for an intriguing discrepancy between increased LA pressure and normal LV end-diastolic pressure despite an absence of mitral stenosis [18–20]. It has also been suggested that both multiple ablation procedures and modern extensive LA ablation techniques beyond pulmonary vein isolation may lead to more pronounced scarring of the LA wall [19, 20]. Accordingly, the stiff LA syndrome might be increasingly recognized in the future as an underlying cause of otherwise unexplained heart failure with elevated LA pressure and pulmonary hypertension after RFCA.

Notably, another recognized technique of ablation for atrial fibrillation, cryoballoon ablation, not only exhibited efficacy similar to RFCA [21], but also induced a comparable extent of LA fibrosis at 3 months after initial pulmonary vein isolation [22]. This observation [22] supports the notion that both RFCA and cryoballoon ablation are likely to have potential to evoke LA scarring and predispose to the stiff LA syndrome.

Interestingly, a novel interventional strategy aimed at LA and LV depressurization in advanced diastolic heart failure by creating a controlled atrial septal defect [23] ("neo-ASD") was recently applied, for the first time, to a patient with the stiff LA syndrome after 3 ablation procedures within the preceding 9 years, presenting as severe dyspnea and signs of right-sided congestion, refractory to diuretics [24]. This approach resulted in a significant clinical improvement [24], which was discussed by Maeder *et al.* [25], who argued that a persistent post-puncture atrial septal defect was a likely explanation of only minor symptoms in their patient with the LA stiff syndrome after multiple ablations, in spite of

a mean pulmonary wedge pressure of 24 mm Hg with large V-waves of 40 mm Hg.

Pre-procedural left atrial stiffness – a predictor of arrhythmia recurrence after catheter ablation for atrial fibrillation

As discussed above, development of excessive LA stiffening in response to RFCA may translate into clinical manifestations of heart failure termed the stiff LA syndrome. However, pre-ablation LA stiffness may also be of relevance, predisposing to the recurrence of atrial fibrillation. Identification of patients at risk of arrhythmia recurrence still poses a challenge. In a study of 700 consecutive patients followed for a mean of 16 months after a first pulmonary vein isolation procedure, Verma *et al.* [26] reported extensive pre-procedural LA scarring (by contact voltage mapping) as the only independent predictor of arrhythmia recurrence. By means of delayed enhancement MRI, Marrouche *et al.* [27] demonstrated that the extent of pre-procedural LA fibrosis was associated with a higher likelihood of atrial fibrillation recurrence in 272 participants of a multicenter study

More recently, Khurram *et al.* [28] investigated the associations between LA pressure-volume relations and the recurrence of atrial fibrillation in 160 patients who underwent RFCA for the first time. The LA pressure-volume diagram consists of 2 loops arranged in a figure-of-eight pattern [28, 29] (Figure 1 A). The LA stiffness index was derived from the LA atrial pressure-volume curve as the ratio of change in LA pressure to the change in LA volume during passive LA filling at the time of RFCA [28] (Figure 1 B). The authors were able to show that an increased value of the pre-ablation LA stiffness index was the only independent predictor of recurrence of atrial fibrillation over a mean follow-up of 10 months [28].

This observation is in accordance with a previous study by Park *et al.* [30], who reported higher pre-ablation maximal LA pressure in 454 patients undergoing RFCA who exhibited the recurrence of atrial fibrillation. Importantly, higher maximal LA pressure was accompanied by higher LA volume, decreased LA appendage emptying velocity and low intracardiac LA electrogram voltage, termed "electroanatomical remodeling of the LA" [30]. Finally, these observations were later confirmed in 334 patients with a structurally and functionally normal heart, in whom pre-ablation LA pulse pressure (measured in sinus rhythm as the difference in LA pressure between the nadir of the X-wave and the peak of the V-wave – a surrogate approximate index of depressed LA compliance) was associated with lower LA electrogram voltage and independently predicted atrial fibrillation recurrence during a mean follow-up of 17 months [31].

Hence, though there are well-recognized factors contributing to atrial fibrillation, such as mitral stenosis, LV dysfunction, coronary artery disease (CAD), hypertension, obesity and aging, the above observations further potentiated the idea that fibrosis in the LA wall can be a crucial link between development of "atrial myopathy" (an anatomical substrate for the onset/persistence of atrial fibrillation) and predisposing conditions, including atrial overload and stretch, inflammation and oxidative stress [32]. Therefore, LA abnormalities detected by various diagnostic techniques – echocardiography (including novel techniques, e.g. speckle-tracking), MRI, cardiac

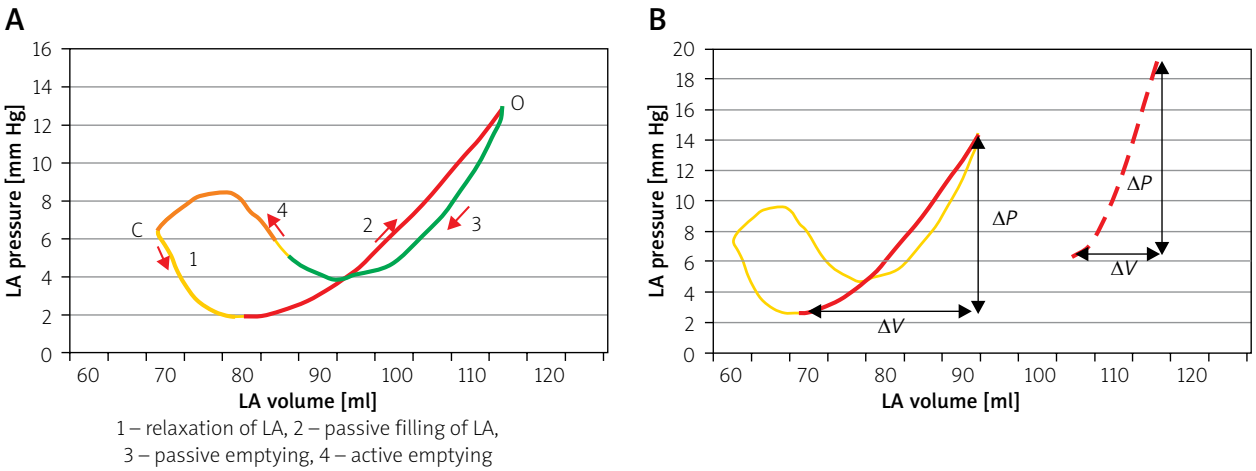

Figure 1. A – Graphical representation of a typical left atrium (LA) pressure–volume loop. Point C is the closure of mitral valve in cardiac systole, and point O is opening of mitral valve at the start of ventricular diastole showing the 4 phases of the LA cardiac cycle. **B** – Measurement of LA stiffness index ($\Delta P/\Delta V$). The slope of phase 2 defines the LA stiffness. The LA stiffness index approximates the slope of phase 2 by taking the ratio of the change in pressure to the change in volume ($\Delta P/\Delta V$) that occurs during the passive filling phase. Here, phase 2 of the 2 patients are highlighted with red color line where solid red line of a compliant LA can be compared with a stiff LA with higher LA pressure (ΔP) and smaller corresponding change in volume (ΔV). Reproduced from Ref. No. 28 with permission of Wolters Kluwer Health, Inc. (license # 4322140443904)

catheterization and intracardiac LA electrogram voltage – are likely to reflect different aspects of LA myopathy, encompassing depressed LA systolic and diastolic function, LA scarring/fibrosis and electrical remodeling. These mechanisms seem to be a plausible explanation for the association of depressed pre-ablation LA compliance with arrhythmia recurrence after RFCA.

Radiofrequency catheter ablation, especially when extensive or repeated, may further potentiate LA fibrosis [18, 19]. Importantly, poor post-procedural scar formation in the ablated area was associated with the recurrence of atrial fibrillation [33, 34]. Intriguingly, these findings apparently contrast with a well-recognized positive relationship between the extent of pre-ablation LA fibrosis and recurrent arrhythmia [27, 35]. Therefore, after RFCA, beneficial "anti-arrhythmic" effects of complete isolation and elimination of the triggers of atrial fibrillation with consequent extensive post-procedural LA scarring can predominate, thereby counteracting the association of pre-procedural LA fibrosis with arrhythmia recurrence. However, with regard to LA hemodynamics, patients with lower pre-ablation LA compliance might also be predisposed to RFCA-induced LA stiffening, manifesting as the stiff LA syndrome. That the stiff LA syndrome develops especially after multiple ablation procedures [18–20], supports this concept. Thus, extensive post-ablation LA scarring appears to be linked to the efficacy of arrhythmia prevention, yet poses a risk of the stiff LA syndrome and symptoms of pulmonary congestion in selected patients. Future research can be aimed at optimizing ablation techniques to achieve the best anti-arrhythmic effect at the lowest possible cost for LA compliance.

Reduced left atrial compliance after left atrial appendage closure

Percutaneous LA appendage (LAA) occlusion has been increasingly utilized for stroke prevention in patients with atrial fibrillation and contraindications to long-term anticoagulation [36]. With the increasing number of interventional LAA occlusion procedures, two questions arise: How does LAA occlusion affect LA compliance? And how do these changes, if present, translate into clinical consequences? Early observations in isolated canine hearts [37] and open-chest dogs [38] revealed that the LA pressure-volume curve was shifted upward and to the left after the exclusion [37] or removal [38] of the LAA, consistent with reduced LA compliance. These results were later confirmed by Tabata *et al.* [39] in 15 patients undergoing LA clamping during cardiac surgery, who also exhibited significant rises in mean LA pressure and maximal LA dimension. Additionally, changes in pulmonary venous and transmitral flow reflected elevated LA pressure, with lower peak second systolic pulmonary flow velocity and accelerated early diastolic mitral flow, owing to an excessive rise in LA pressure prior to mitral valve opening. Importantly, similar changes, i.e. elevated mean LA pressure and maximal LA volume, were recently reported in 58 consecutive patients after successful LAA occlusion [40]. The authors linked these effects to probable reductions in LA compliance with consequent increases in LA pressure after the procedure [40]. Finally, the same mechanism was proposed as an explanation of almost 4-fold higher risk of early postoperative atrial fibrillation in 10,633 subjects who underwent prophylactic surgical exclusion of the LAA during cardiac surgery [41]. The latter report represents a brilliant example of how an early experimental observation by Davis *et al.* [37], i.e. 2.6 times higher compliance of the LAA compared to the remaining LA chamber, can be helpful to understand the basis of symptoms in real-world patients almost 30 years later [41].

In summary, both RFCA and LAA closure are likely to induce reductions in LA compliance, which seems an inevitable consequence of these procedures. More importantly, the incidence of its symptomatic presentation – post-ablation stiff LA syndrome – is rare, and the syndrome has not yet been described after LAA closure. Nevertheless, keeping in mind the growing number of LAA occlusion devices, it does not seem implausible that such a case may emerge in the future. Admittedly, Clare *et al.* [42] observed the stiff LA syndrome in a patient after surgical epicardial radiofrequency pulmonary vein isolation and LAA resection, followed by re-isolation of pulmonary veins by endocardial RFCA 5 years later. However, the combination of various procedures made it impossible to identify the main contributor to LA scarring.

Hence, irrespective of the type of LA-related interventions, RFCA or LAA closure, proper preoperative identification of patients at risk for clinical manifestations of post-procedural LA stiffening should be a focus of further research.

Acknowledgments

Joanna B. Hrabia and Bernadeta Chyrchel – equal contribution. Olga Kruszelnicka and Andrzej Surdacki – joint senior authors on this work.

Conflict of interest

The authors declare no conflict of interest.

References

1. Thomas JD, Wilkins GT, Choong CY, et al. Inaccuracy of mitral pressure half-time immediately after percutaneous mitral valvotomy. Dependence on transmitral gradient and left atrial and ventricular compliance. Circulation 1988; 78: 980-93.
2. Hatle L, Angelsen B, Tromsdal A. Noninvasive assessment of atrioventricular pressure half-time by Doppler ultrasound. Circulation 1979; 60: 1096-104.
3. Flachskampf FA, Weyman AE, Guerrero JL, Thomas JD. Calculation of atrioventricular compliance from the mitral flow profile: analytic and in vitro study. J Am Coll Cardiol 1992; 19: 998-1004.

4. Schwammenthal E, Vered Z, Agranat O, et al. Impact of atrioventricular compliance on pulmonary artery pressure in mitral stenosis: an exercise echocardiographic study. Circulation 2000; 102: 2378-84.
5. Kim HK, Kim YJ, Hwang SJ, et al. Hemodynamic and prognostic implications of net atrioventricular compliance in patients with mitral stenosis. J Am Soc Echocardiogr 2008; 21: 482-6.
6. Thomas JD, Choong CY, Flachskampf FA, Weyman AE. Analysis of the early transmitral Doppler velocity curve: effect of primary physiologic changes and compensatory preload adjustment. J Am Coll Cardiol 1990; 16: 644-55.
7. Li M, Déry JP, Dumesnil JG, et al. Usefulness of measuring net atrioventricular compliance by Doppler echocardiography in patients with mitral stenosis. Am J Cardiol 2005; 96: 432-5.
8. Nunes MC, Hung J, Barbosa MM, et al. Impact of net atrioventricular compliance on clinical outcome in mitral stenosis. Circ Cardiovasc Imaging 2013; 6: 1001-8.
9. Jung MH, Jung HO, Lee JW, Young HJ. Decreases in left atrial compliance during early-stage exercise are related to exercise intolerance in asymptomatic significant mitral stenosis. Echocardiography 2017; 34: 1633-9.
10. Mahfouz RA, Elawady W, Hossein E, Yosri A. Impact of atrioventricular compliance on clinical outcome of patients undergoing successful percutaneous balloon mitral valvuloplasty. Echocardiography 2013; 30: 1187-93.
11. Nunes MCP, Tan TC, Elmariah S, et al. Net atrioventricular compliance is an independent predictor of cardiovascular death in mitral stenosis. Heart 2017; 103: 1891-8.
12. Reant P, Lafitte S, Jaïs P, et al. Reverse remodeling of the left cardiac chambers after catheter ablation after 1 year in a series of patients with isolated atrial fibrillation. Circulation 2005; 112: 2896-903.
13. Müller H, Noble S, Keller PF, et al. Biatrial anatomical reverse remodeling after radiofrequency catheter ablation for atrial fibrillation: evidence from real-time three dimensional echocardiography. Europace 2008; 10: 1073-8.
14. Choi JI, Park SM, Park JS, et al. Changes in left atrial structure and function after catheter ablation and electrical cardioversion for atrial fibrillation. Circ J 2008; 72: 2051-7.
15. Witt CM, Fenstad ER, Cha YM, et al. Increase in pulmonary arterial pressure after atrial fibrillation ablation: incidence and associated findings. J Interv Card Electrophysiol 2014; 40: 47-52.
16. Hof IE, Vonken EJ, Velthuis BK, et al. Impact of pulmonary vein antrum isolation on left atrial size and function in patients with atrial fibrillation. J Interv Card Electrophysiol 2014; 39: 201-9.
17. Pilote L, Huttner I, Marpole D, Sniderman A. Stiff left atrial syndrome. Can J Cardiol 1988; 4: 255-7.
18. Gibson DN, Di Biase L, Mohanty P, et al. Stiff left atrial syndrome after catheter ablation for atrial fibrillation: clinical characterization, prevalence, and predictors. Heart Rhythm 2011; 8: 1364-71.
19. Shoemaker MB, Hemnes AR, Robbins IM, et al. Left atrial hypertension after repeated catheter ablations for atrial fibrillation. J Am Coll Cardiol 2011; 57: 1918-9.
20. Yang Y, Liu Q, Wu Z, et al. Stiff left atrial syndrome: a complication undergoing radiofrequency catheter ablation for atrial fibrillation. J Cardiovasc Electrophysiol 2016; 27: 884-9.
21. Ma H, Sun D, Luan H, et al. Efficacy and safety of cryoballoon ablation versus radiofrequency catheter ablation in atrial fibrillation: an updated meta-analysis. Adv Interv Cardiol 2017; 13: 240-9.
22. Khurram IM, Catanzaro JN, Zimmerman S, et al. MRI evaluation of radiofrequency, cryothermal, and laser left atrial lesion formation in patients with atrial fibrillation. Pacing Clin Electrophysiol 2015; 38: 1317-24.
23. Toth GG, Vanderheyden M, Bartunek J. Novel device-based interventional strategies for advanced heart failure. Adv Interv Cardiol 2016; 12: 13-6.
24. Chandrashekar P, Park JY, Al-Hijji MA, et al. Atrial septostomy to treat stiff left atrium syndrome. Circ Heart Fail 2017; 10: e004160.
25. Maeder MT, Nägele R, Rohner P, Weilenmann D. Pulmonary hypertension in stiff left atrial syndrome: pathogenesis and treatment in one. ESC Heart Fail 2018; 5: 189-92.
26. Verma A, Wazni OM, Marrouche NF, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol 2005; 45: 285-92.
27. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA 2014; 311: 498-506.
28. Khurram IM, Maqbool F, Berger RD, et al. Association between left atrial stiffness index and atrial fibrillation recurrence in patients undergoing left atrial ablation. Circ Arrhythm Electrophysiol 2016; 9: e003163.
29. Pagel PS, Kehl F, Gare M, et al. Mechanical function of the left atrium: new insights based on analysis of pressure-volume relations and Doppler echocardiography. Anesthesiology 2003; 98: 975-94.
30. Park J, Joung B, Uhm JS, et al. High left atrial pressures are associated with advanced electroanatomical remodeling of left atrium and independent predictors for clinical recurrence of atrial fibrillation after catheter ablation. Heart Rhythm 2014; 11: 953-60.
31. Park J, Yang PS, Kim TH, et al. Low left atrial compliance contributes to the clinical recurrence of atrial fibrillation after catheter ablation in patients with structurally and functionally normal heart. PLoS One 2015; 10: e0143853.
32. Goldberger JJ, Arora R, Green D, et al. Evaluating the atrial myopathy underlying atrial fibrillation: identifying the arrhythmogenic and thrombogenic substrate. Circulation 2015; 132: 278-91.
33. Peters DC, Wylie JV, Hauser TH, et al. Recurrence of atrial fibrillation correlates with the extent of post-procedural late gadolinium enhancement: a pilot study. JACC Cardiovasc Imaging 2009; 2: 308-16.
34. Parmar BR, Jarrett TR, Kholmovski EG, et al. Poor scar formation after ablation is associated with atrial fibrillation recurrence. J Interv Card Electrophysiol 2015; 44: 247-56.
35. Khurram IM, Habibi M, Gucuk Ipek E, et al. Left atrial LGE and arrhythmia recurrence following pulmonary vein isolation for paroxysmal and persistent AF. JACC Cardiovasc Imaging 2016; 9: 142-8.
36. Grygier M, Olasińska-Wiśniewska A, Araszkiewicz A, et al. The Watchman FLX – a new device for left atrial appendage occlusion – design, potential benefits and first clinical experience. Adv Interv Cardiol 2017; 13: 62-6.
37. Davis CA 3rd, Rembert JC, Greenfield JC Jr. Compliance of left atrium with and without left atrium appendage. Am J Physiol 1990; 259: H1006-8.
38. Hoit BD, Shao Y, Tsai LM, et al. Altered left atrial compliance after atrial appendectomy. Influence on left atrial and ventricular filling. Circ Res 1993; 72: 167-75.

39. Tabata T, Oki T, Yamada H, et al. Role of left atrial appendage in left atrial reservoir function as evaluated by left atrial appendage clamping during cardiac surgery. Am J Cardiol 1998; 81: 327-32.
40. Luani B, Groscheck T, Genz C, et al. Left atrial enlargement and clinical considerations in patients with or without a residual interatrial shunt after closure of the left atrial appendage with the WATCHMAN™-device. BMC Cardiovasc Disord 2017; 17: 294.
41. Melduni RM, Schaff HV, Lee HC, et al. Impact of left atrial appendage closure during cardiac surgery on the occurrence of early postoperative atrial fibrillation, stroke, and mortality: a propensity score-matched analysis of 10 633 patients. Circulation 2017; 135: 366-78.
42. Clare GC, Margulescu AD, Leong FT. Stiff left atrial syndrome following left atrial appendage resection and multiple ablations for atrial fibrillation. Heart 2013; 99: 508.